

# GSK- 873,140 (aplaviroc)



**Drug Class:** Entry and Fusion Inhibitors

## Drug Description

GSK-873,140, also known as 873140, is an orally bioavailable spirodiketopiperazine (SDP) CCR5 antagonist that binds specifically to human CCR5 receptors. [1] [2]

## HIV/AIDS-Related Uses

GSK-873,140 is an entry inhibitor in Phase III studies for the treatment of HIV-1 infection. These studies have been halted because of continued liver toxicities. Phase III enrollment and Phase IIb studies were suspended in September 2005 when two treatment-naïve patients experienced severe liver toxicity. In October 2005, liver enzyme and total bilirubin elevations were observed in a treatment-experienced patient in a Phase III trial, leading to the termination of all studies. No further studies are planned.

Patients receiving GSK-873,140 should be switched to an alternative treatment regimen. Some patients deriving benefit from GSK-873,140 may remain on the treatment under physician supervision but must be monitored closely for signs and symptoms of liver toxicity.[3]

## Pharmacology

CCR5 is a major chemokine receptor that HIV uses to enter CD4 cells.[4] GSK-873,140 is an SDP derivative that specifically blocks the binding of macrophage inflammatory protein 1-alpha (MIP-1a) to CCR5, potentially blocks HIV-1 glycoprotein 120 (gp120) binding to CCR5, and preserves RANTES and MIP-1b binding to CCR5.[5] [6] Although other CCR5 inhibitor binding sites are often found in the transmembrane domain, GSK-873,140 CCR5 binding sites appear clustered around the ECL2 interface.[7] Limited variability in anti-HIV activity has been observed against different R5-tropic isolates in peripheral blood mononuclear cells (PBMCs) from multiple donors.[8] GSK-873,140 shows substantial occupancy of CCR5 binding sites at in vivo-attainable concentrations and a longer binding duration than other CCR5 inhibitors currently under investigation, such as UK-427,857 and SCH-D.[9]

GSK-873,140 in vitro studies suggest that the drug has prolonged CCR5 receptor occupancy, with an offset half-life of more than 100 hours. In vivo studies have shown that 873140 exhibits greater than 97% CCR5 receptor occupancy in blood during repeat oral administration and sustains viral suppression for 24 to 48 hours after therapy discontinuation.[10]

Receptor occupancy and half-life were quantified in a 1-day, dose-ranging study of GSK-873,140 in 8 HIV uninfected and 31 HIV infected patients. After 7 days of 600 mg twice-daily therapy, median CD4 cell CCR5 receptor occupancy was 98%; final post-treatment analysis on Day 13 suggested occupancy half-life was 127 hours after the last administered dose. HIV infected patients received 10 days of 873140 at doses of 200 or 600 mg twice daily or 200 or 400 mg once daily. After 10 days of therapy, receptor occupancy was greater than 95% in all groups; final post-treatment analysis on Day 24 estimated that occupancy half-life was 122 hours after the last administered dose. Higher doses tended toward longer occupancy duration. After therapy was discontinued and plasma drug levels became undetectable, receptor occupancy remained greater than 50% for approximately 5 days.[11]

In a Phase I/II randomized, double-blind, placebo-controlled, dose-ranging monotherapy study, GSK-873,140 was given as monotherapy for 10 days to HIV-1 infected antiretroviral-naïve and -experienced patients at doses of 200 or 600 mg twice daily and 200 or 400 mg once daily (8 receiving drug, 2 receiving placebo per arm). All doses were given with a moderate fat meal. Antiretroviral-experienced patients abstained from treatment for 12 weeks prior to entry. All patients had a viral load of 5,000 copies/mL or greater and a CD4 count nadir greater than 200 cells/mm<sup>3</sup>. All patients were infected with R5-tropic HIV. A greater than 10-fold, dose-dependent, viral load decrease was observed in patients taking 400 mg once daily and 200 or 600 mg twice daily. The lowest viral load was observed between 24 and 36 hours after therapy discontinuation, suggesting a long CCR5 receptor occupancy. Evidence of viral tropism conversion to dual-tropic virus was seen in one patient on Day 10; virus reverted back to

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## Pharmacology (cont.)

R5-tropic virus on Day 24; analysis is ongoing.[12]

In a multiple-dose study conducted in 70 fasting, HIV uninfected adults, median maximum plasma concentration (C<sub>max</sub>) for GSK-873,140 was 24 ng/mL at a 200 mg twice-daily dose and 100 ng/mL at an 800 mg twice-daily dose. Area under the concentration-time curve (AUC) was 127 ng-h/mL for the 200 mg twice-daily dose and 329 ng-h/mL for the 800 mg twice-daily dose. Receptor occupancy at 24 hours after a single dose ranged from 68% to 88%, increasing to greater than 97% at 2 and 12 hours after multiple doses.[13]

## Adverse Events/Toxicity

In early studies, GSK-873,140 appeared well tolerated when taken orally. The most common adverse effects noted in a 10-day, GSK-873,140 monotherapy, dose-ranging study were loose stools, diarrhea, abdominal pain, nausea, and flatulence. Headache, dizziness, and fatigue also occurred. Most adverse effects resolved within three days.[14]

Mild to moderate abdominal cramping, nausea, and diarrhea were observed in a dose-escalation study; no serious Grade 3 or 4 adverse effects were reported. No changes in laboratory or electrocardiographic parameters were observed.[15]

Coadministration of lopinavir/ritonavir and GSK-873,140 also resulted in minor, self-limiting gastrointestinal complaints but no significant laboratory abnormalities.[16]

Severe liver toxicity developed in two treatment-naïve patients in Phase IIb studies of GSK-873,140, and liver enzymes and total bilirubin increased in a treatment-experienced patient in a Phase III trial. Because of these observed liver toxicities, all studies of GSK-873,140 have been halted.[17]

## Drug and Food Interactions

Administration of GSK-873,140 with food increases the AUC and C<sub>max</sub> of 200 and 800 mg twice daily doses by 1.7- and 2.2-fold,

respectively.[18]

GSK-873,140 displays additive or synergistic activity when combined with other antiretroviral agents. In PBMCs exposed to R5-tropic HIV, GSK-873,140 had synergistic effects when combined with zidovudine, nevirapine, indinavir, and enfuvirtide, and additive effects when combined with another investigational CCR5 antagonist, SCH-C. Potent synergism was observed in PBMCs exposed to dual-tropic HIV and treated with GSK-873,140 when combined with investigational CXCR4 inhibitors AMD3100 or TE14011. No antagonistic effects or synergistic cellular toxicities were observed in vitro.[19] [20]

GSK-873,140 is a cytochrome P450-3A substrate in vitro. A trial of eight HIV uninfected adults examined the effect of ritonavir and lopinavir/ritonavir on GSK-873,140 over three different periods. All patients were initially given a 50 mg test dose of GSK-873,140 with or without a single 100 mg dose of ritonavir. In period one, patients received 400 mg GSK-873,140 twice daily for 7 days; in period two, lopinavir/ritonavir 400/100 mg twice daily for 14 days; in period three, coadministration twice daily for 7 days. All doses were administered with a moderate fat meal. A single ritonavir dose increased the GSK-873,140 test dose AUC and C<sub>max</sub> 2.1- and 2.3-fold, respectively. Coadministration for 7 days resulted in significant increases of 7.7-, 6.2-, and 7.1-fold in AUC, C<sub>max</sub>, and minimum plasma concentration (C<sub>min</sub>), respectively. No changes in lopinavir parameters but small increases in ritonavir parameters were observed.[21]

## Clinical Trials

For information on clinical trials that involve GSK-873,140 (aplaviroc), visit the ClinicalTrials.gov web site at <http://www.clinicaltrials.gov>. In the Search box, enter: GSK-873,140 (aplaviroc) AND HIV Infections.

## Dosing Information

Mode of Delivery: Oral.[22]

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## Dosing Information (cont.)

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Dosage Form: GSK-873,140 has been studied in clinical trials using once or twice daily doses of 50, 200, 400, 600, or 800 mg.[23]

## Chemistry

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CAS Name: Benzoic acid,4-(4-(((3R)-1-butyl-3-((R)-cyclohexylhydroxymethyl)-2,5-dioxo-1,4,9-triazaspiro(55)undec-9-yl)methyl)phenoxy)-[24]

CAS Number: 461443-59-4[25]

Molecular formula: C33-H43-N3-O6[26]

C68%, H8%, N7%, O17%[27]

Molecular weight: 577[28]

## Other Names

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AK-602[29]

ONO4128[30]

GW873140[31]

AK602[32]

873,140[33]

873140[34]

## Further Reading

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Barber CG. CCR5 antagonists for the treatment of HIV. Curr Opin Investig Drugs. 2004 Aug;5(8):851-61. Review. PMID: 15600241

Maeda K, Nakata H, Koh Y, Miyakawa T, Ogata H, Takaoka Y, Shibayama S, Sagawa K, Fukushima D, Moravek J, Koyanagi Y, Mitsuya H. Spirodiketopiperazine-based CCR5 inhibitor which preserves CC-chemokine/CCR5 interactions and exerts potent activity against R5 human immunodeficiency virus type 1 in vitro. J Virol. 2004 Aug;78(16):8654-62. PMID: 15280474

Nakata H, Maeda K, Miyakawa T, Shibayama S, Matsuo M, Takaoka Y, Ito M, Koyanagi Y, Mitsuya H. Potent anti-R5 human immunodeficiency virus type 1 effects of a CCR5 antagonist, AK602/ONO4128/GW873140, in a novel human peripheral blood mononuclear cell nonobese diabetic-SCID, interleukin-2 receptor gamma-chain-knocked-out AIDS mouse model. J Virol. 2005 Feb;79(4):2087-96. PMID: 15681411

Seibert C, Sakmar TP. Small-molecule antagonists of CCR5 and CXCR4: a promising new class of anti-HIV-1 drugs. Curr Pharm Des. 2004;10(17):2041-62. Review. PMID: 15279544

## Manufacturer Information

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GSK-873,140 (aplaviroc)  
GlaxoSmithKline  
5 Moore Drive  
Research Triangle Park, NC 27709  
(888) 825-5249

## For More Information

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Contact your doctor or an AIDSinfo Health Information Specialist:

- Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET
- Via Live Help: [http://aidsinfo.nih.gov/live\\_help](http://aidsinfo.nih.gov/live_help) Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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## References

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1. Intl AIDS Conf - 15th, 2004. Abstract WeOrA1231.
2. Conf Retroviruses Opportunistic Infect. - 12th, 2005. Abstract 77.
3. GlaxoSmithKline - GlaxoSmithKline Terminates Patient Enrollment for Phase 3 Studies of Investigational HIV Entry Inhibitor Aplaviroc (GW873140) [Press Release, October 24, 2005]. Available at: <http://www.gsk.com/media/pressreleases.htm>. Accessed 11/10/05.
4. Conf Retroviruses Opportunistic Infect. - 12th, 2005. Abstract 543.
5. J Virol - 2004 Aug;78(16):8654-62
6. Mol Pharmacol - 2005 Feb 3; Epub ahead of print
7. Conf Retroviruses Opportunistic Infect. - 11th, 2004. Poster 540.
8. Intl AIDS Conf - 15th, 2004. Abstract WeOrA1231.
9. Interscience Conf on Antimicrobial Agents and Chemotherapy - 44th, 2004. Abstract H-211.
10. Conf Retroviruses Opportunistic Infect. - 12th, 2005. Abstract 77.
11. Conf Retroviruses Opportunistic Infect. - 12th, 2005. Abstract 77.
12. Interscience Conf on Antimicrobial Agents and Chemotherapy - 44th, 2004. Abstract H-1137b.
13. Conf Retroviruses Opportunistic Infect. - 11th, 2004. Abstract 139.
14. Interscience Conf on Antimicrobial Agents and Chemotherapy - 44th, 2004. Abstract H-1137b.
15. Conf Retroviruses Opportunistic Infect. - 11th, 2004. Abstract 139.
16. Conf Retroviruses Opportunistic Infect. - 12th, 2005. Abstract 664.
17. GlaxoSmithKline - GlaxoSmithKline Terminates Patient Enrollment for Phase 3 Studies of Investigational HIV Entry Inhibitor Aplaviroc (GW873140) [Press Release, October 24, 2005]. Available at: <http://www.gsk.com/media/pressreleases.htm>. Accessed 11/10/05.
18. Conf Retroviruses Opportunistic Infect. - 11th, 2004. Abstract 139.
19. Intl AIDS Conf - 15th, 2004. Abstract WeOrA1231.
20. Conf Retroviruses Opportunistic Infect. - 12th, 2005. Abstract 543.
21. Conf Retroviruses Opportunistic Infect. - 12th, 2005. Abstract 664.
22. Conf Retroviruses Opportunistic Infect. - 12th, 2005. Abstract 77.
23. Conf Retroviruses Opportunistic Infect. - 11th, 2004. Abstract 139.
24. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp>. Accessed 02/15/05.
25. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp>. Accessed 02/15/05.
26. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp>. Accessed 02/15/05.
27. Calculation. -
28. Calculation. -
29. ChemIDplus - Available at: <http://chem.sis.nlm.nih.gov/chemidplus/chemidlite.jsp>. Accessed 02/15/05.

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- 30. Conf Retroviruses Opportunistic Infect. - 12th, 2005. Abstract 543.
- 31. Conf Retroviruses Opportunistic Infect. - 12th, 2005. Abstract 543.
- 32. J Virol - 2004 Aug;78(16):8654-62
- 33. Intl AIDS Conf - 15th, 2004. Abstract WeOrA1231.
- 34. Interscience Conf on Antimicrobial Agents and Chemotherapy - 44th, 2004. Abstract H-211.